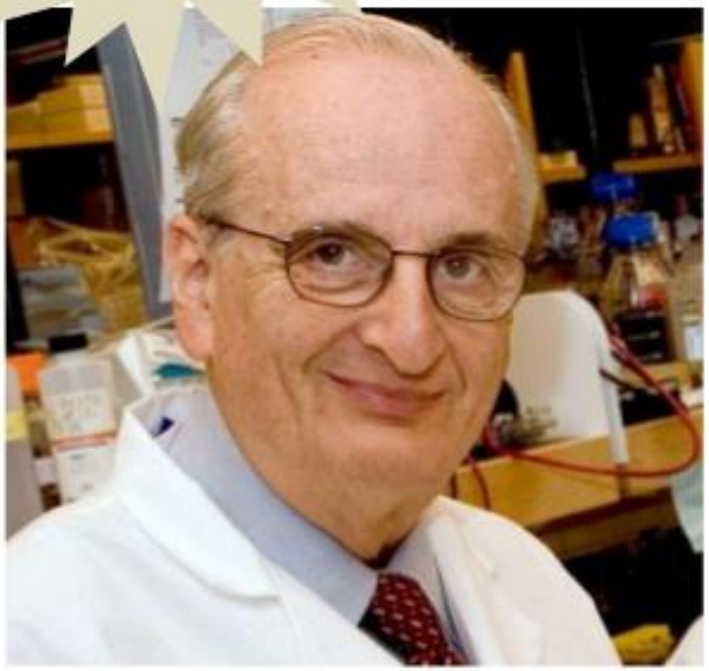
History of Angiogenesis

New field



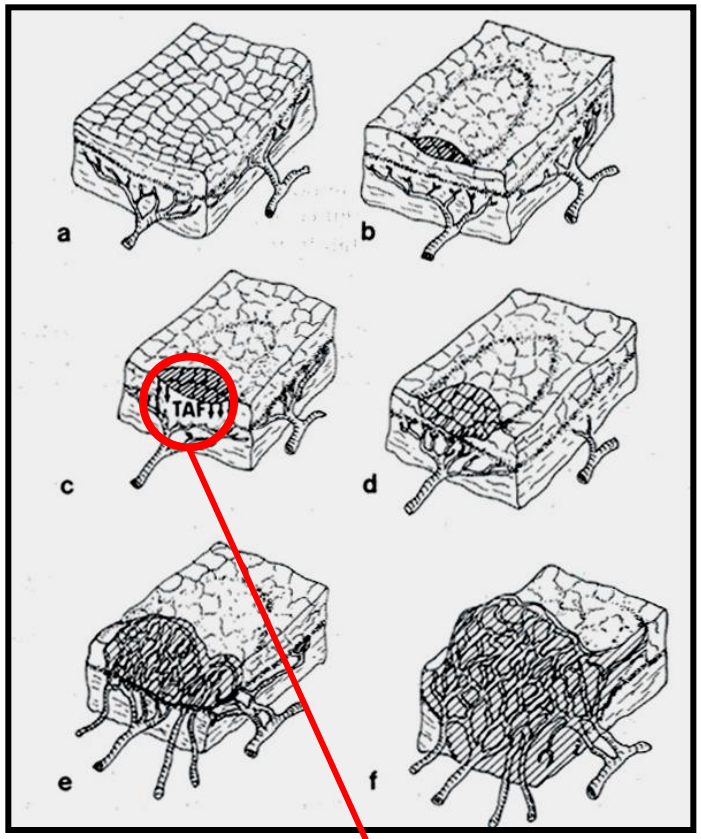
Judah Folkman
1933 - 2008

In 1971,
when he reported - all
cancer tumors are
angiogenesis-dependent.

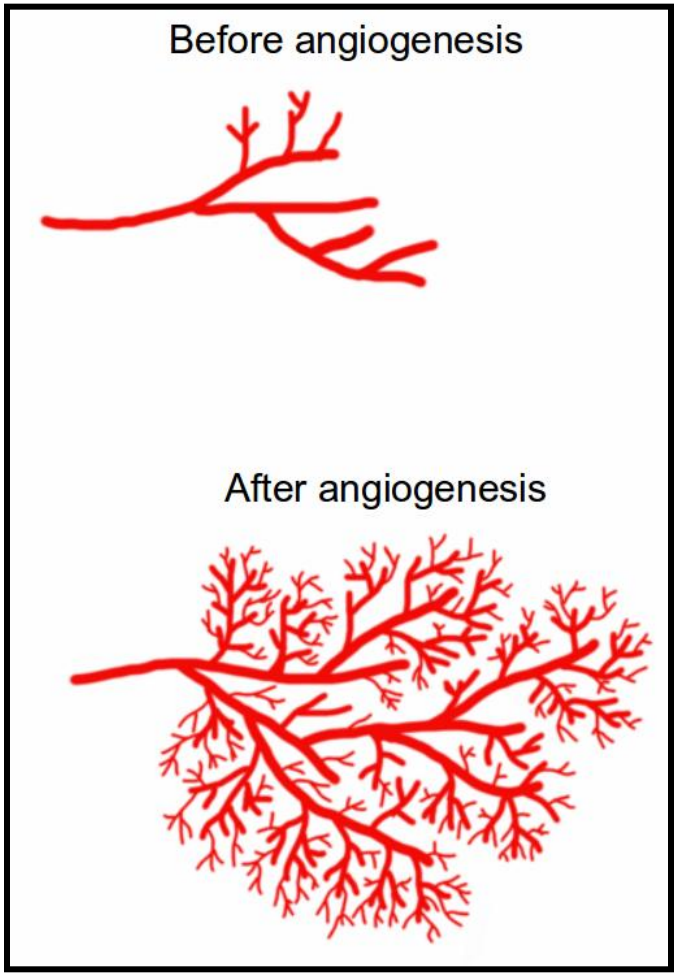
It was not readily accepted.

But after a decade people
recognize a close relation between
tumor and angiogenesis.

It leads to development of
a new field named
"Angiogenesis" in science.



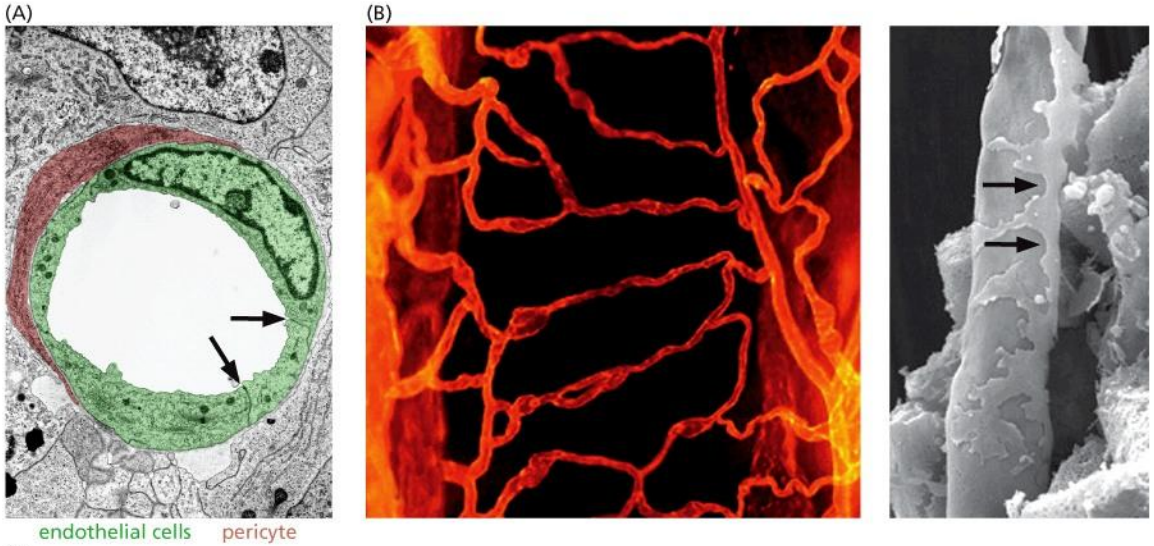
Folkman, 1975



TAF: Tumor Angiogenesis Factors

https://www.youtube.com/watch?v=Qu2DVcxCLCs

Microvessels in normal tissue



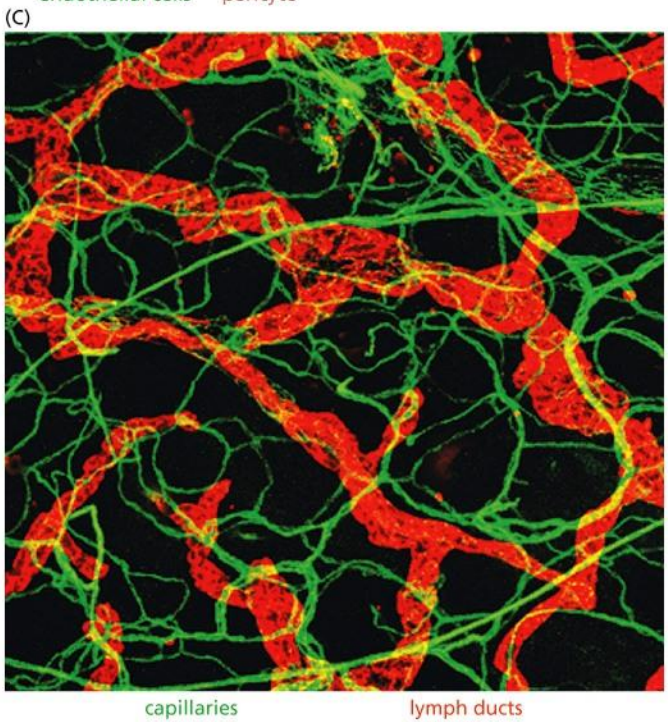
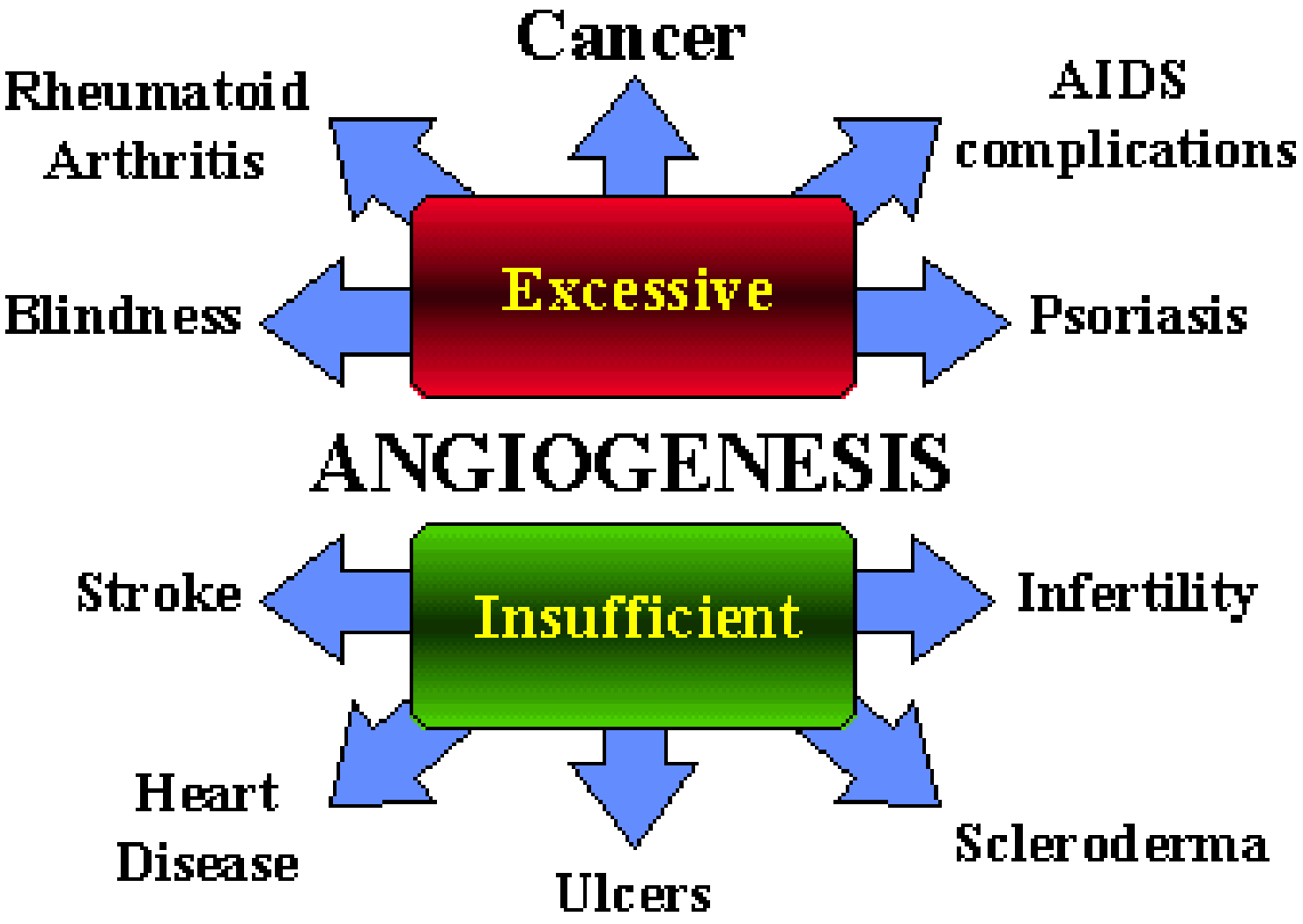


Figure 13.7 The Biology of Cancer (© Garland Science 2014)

ANGIOGENESIS IS A PHYSIOLOGICAL PROCESS


Cancer
Rheumatoid Arthritis
AIDS complications
Excessive
Blindness
Psoriasis
ANGIOGENESIS
Stroke
Insufficient
Infertility
Heart Disease
Ulcers
Scleroderma

Microvessels in a tumor

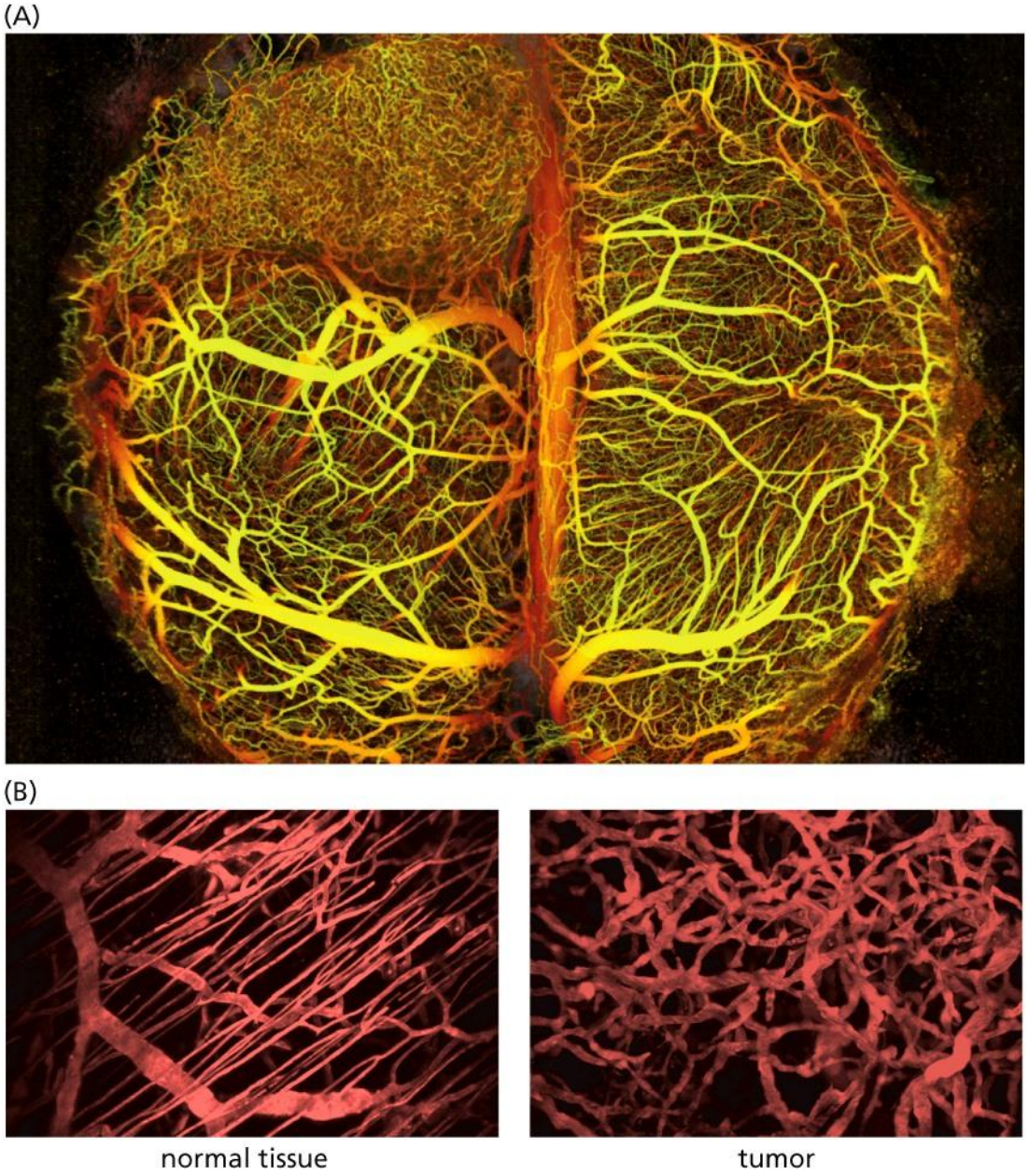
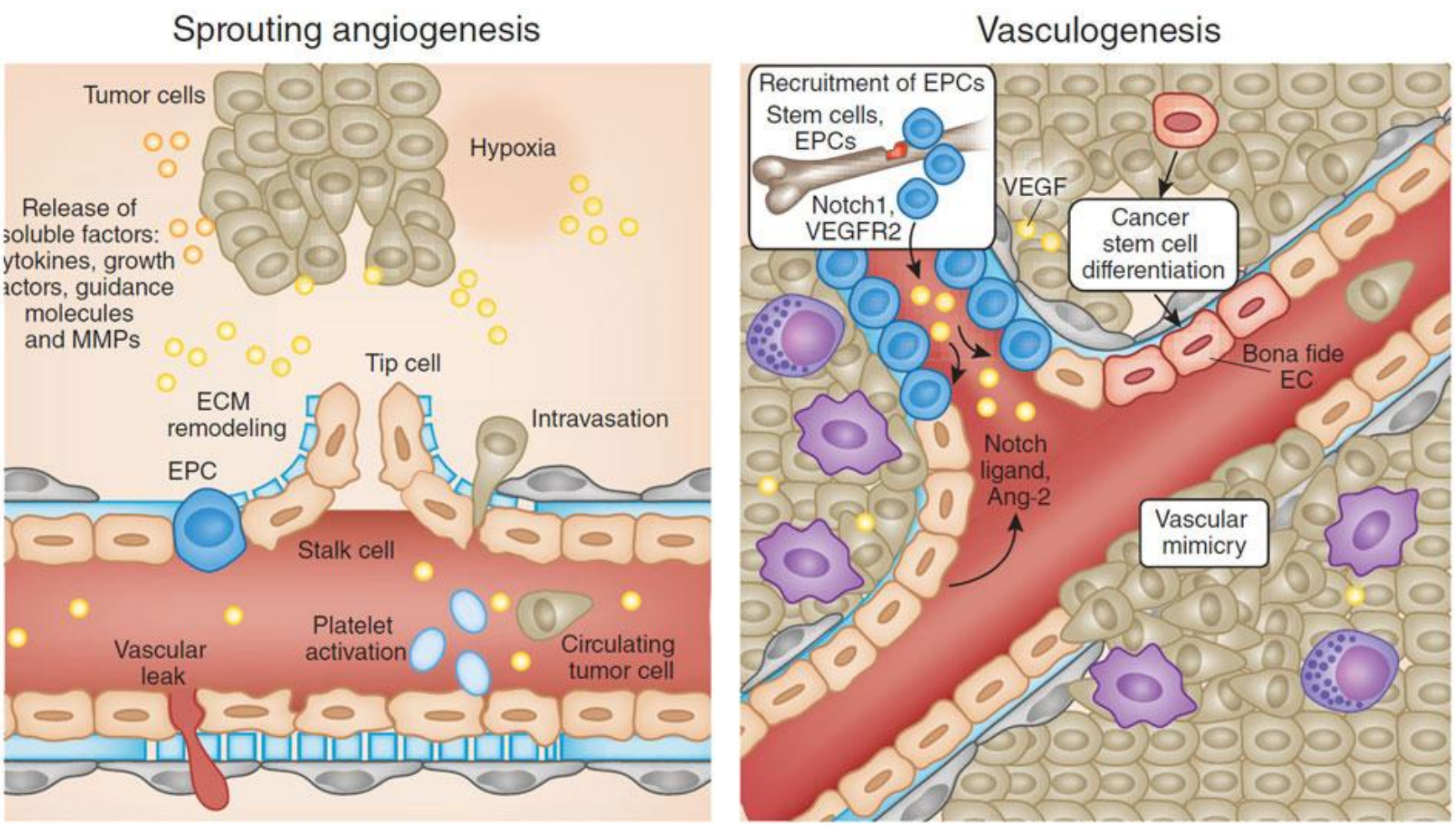
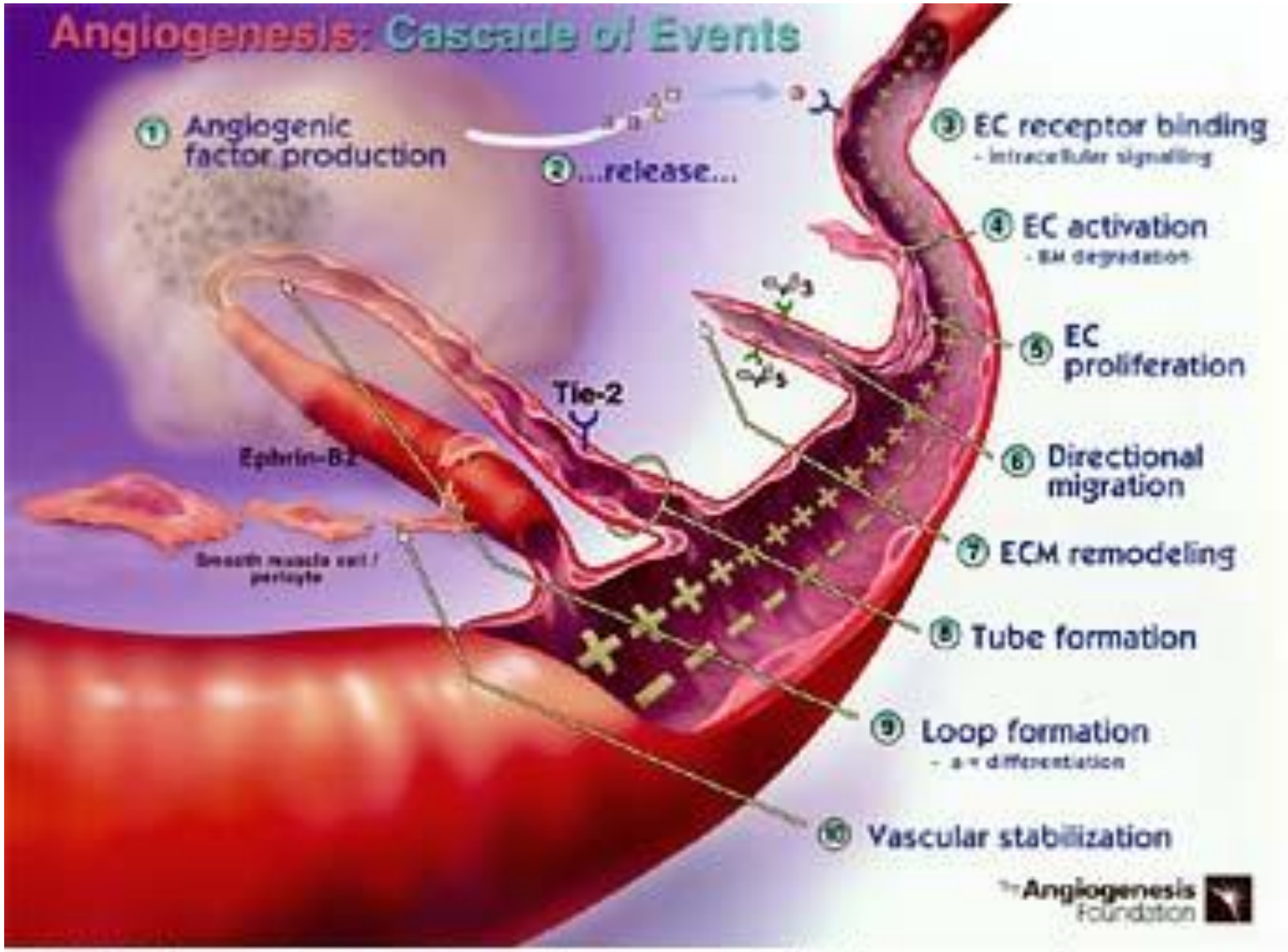
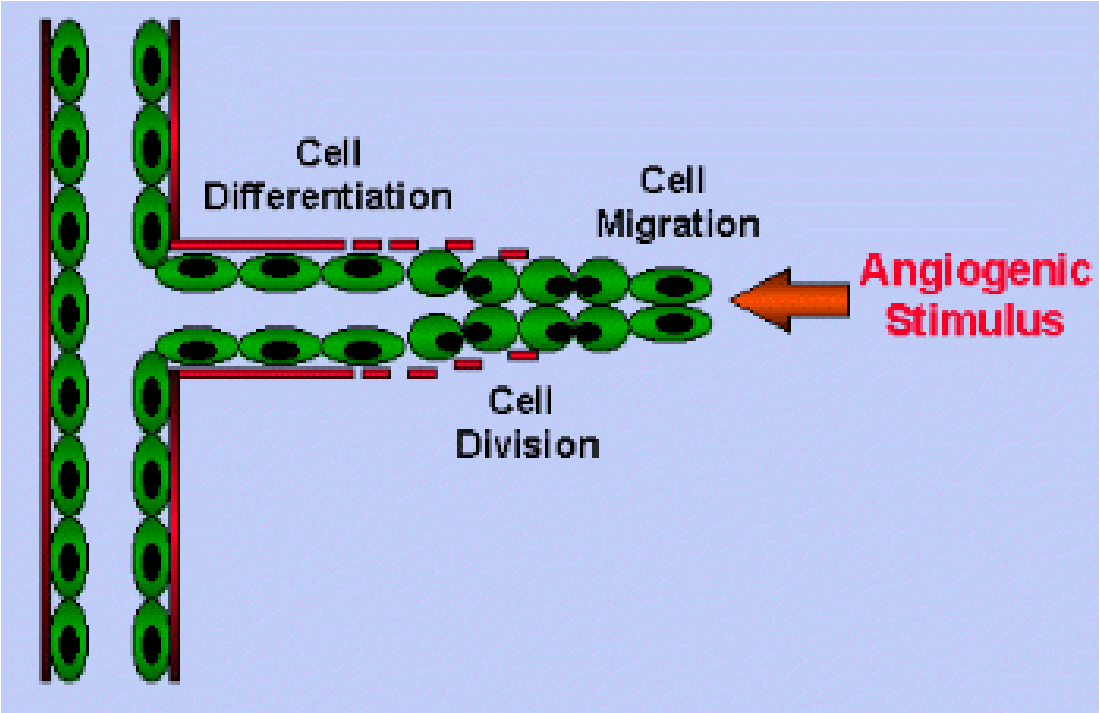


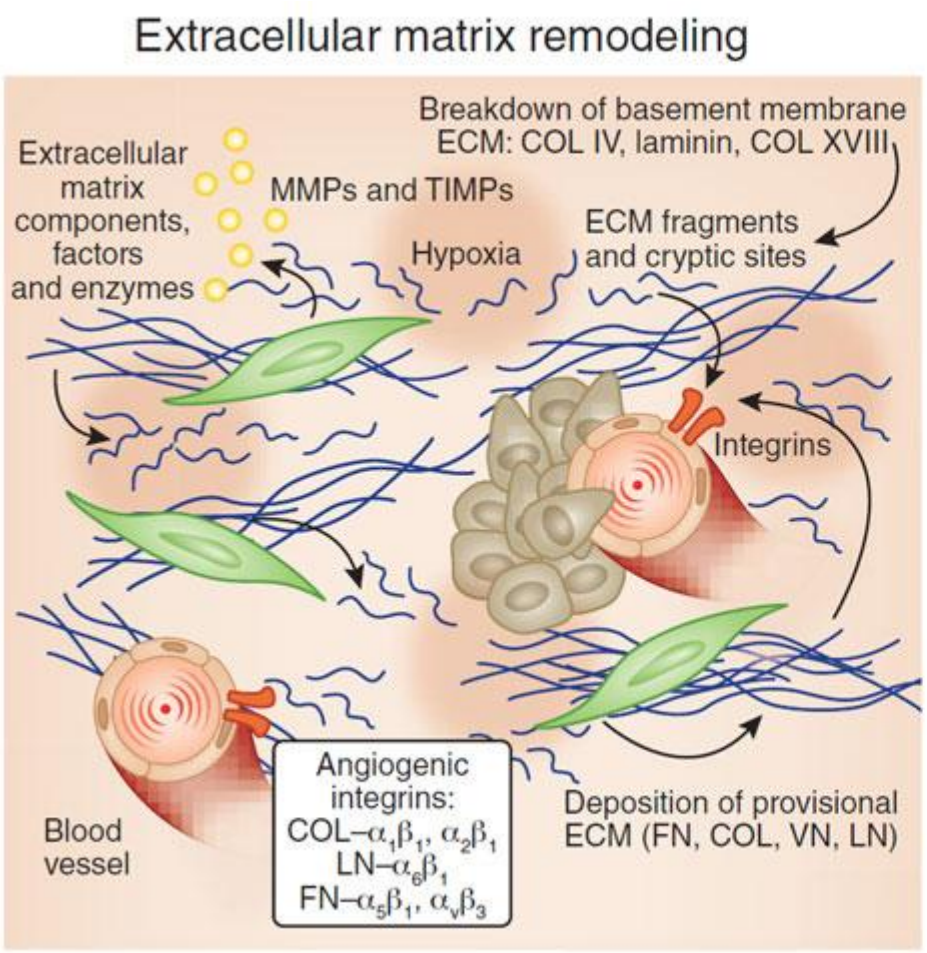
Figure 13.33 The Biology of Cancer (© Garland Science 2014)

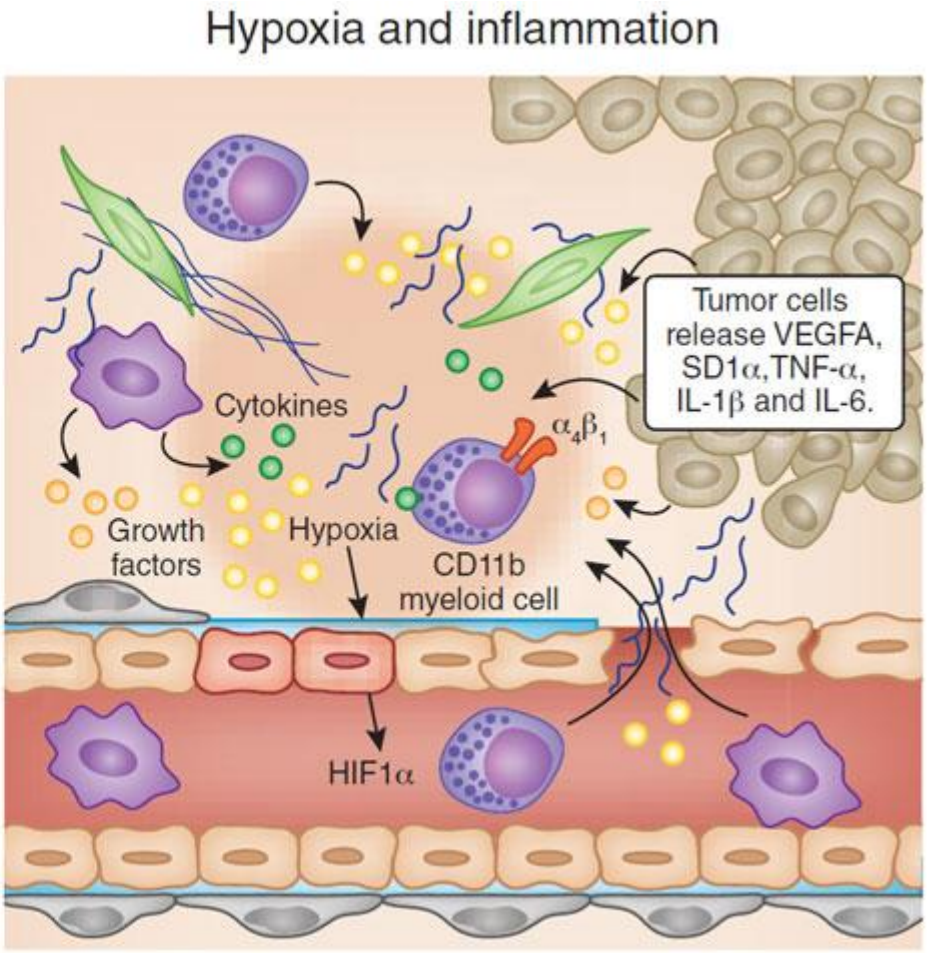


The combination of stimulatory signals within the tumor microenvironment prompts changes in multiple cell types. Perivascular cells detach from the mature blood vessels, compromising their integrity, permitting their remodeling and promoting an activated phenotype. Once the vascular barrier is disrupted, multiple cell types are exposed to angiogenic and inflammatory stimuli to escalate the response. Platelets are recruited to sites of exposed basement membrane, where they become activated and release their stores of stimulatory factors into the tumor microenvironment. Endothelial progenitor cells (EPCs) and myeloid cells from the bone marrow move to the perceived wound, where they release even more soluble factors locally. Cancer stem cells can differentiate to become bona fide endothelial cells, or tumor cells can physically participate in the formation of new vessels through vascular mimicry. However, the escalation of this response does not lead to the production of mature and proper blood vessels that improve the initial hypoxic situation because the tumor microenvironment is characterized by pockets of hypoxia amid the leaky and tortuous blood vessels. This environment also makes the tumor cells more invasive, allowing them to intravasate into the vasculature or lymphatics for metastasis to distant tissues. Effective strategies for cancer therapy must consider targets on multiple cell types and address issues of poor drug delivery in the leaky and poorly perfused tumor microenvironment (Wei & Cheresh, 2011).

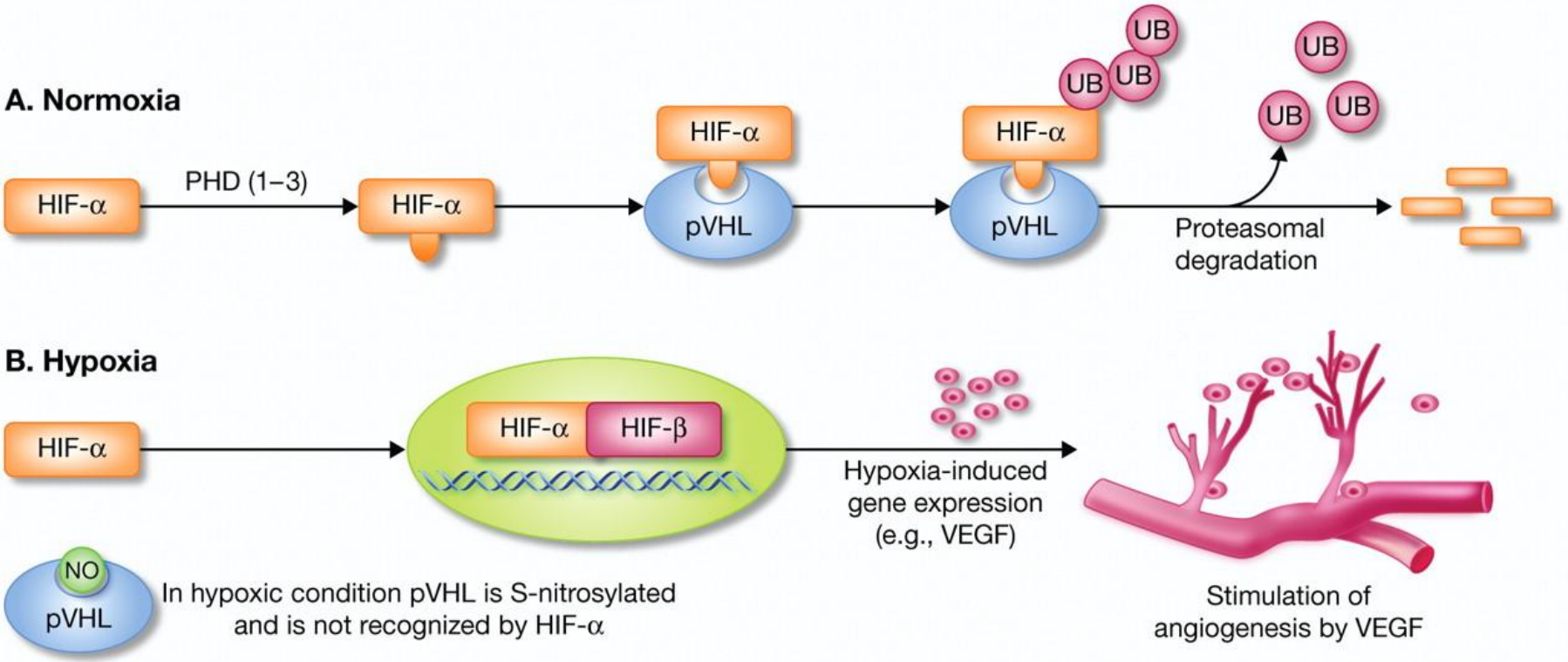


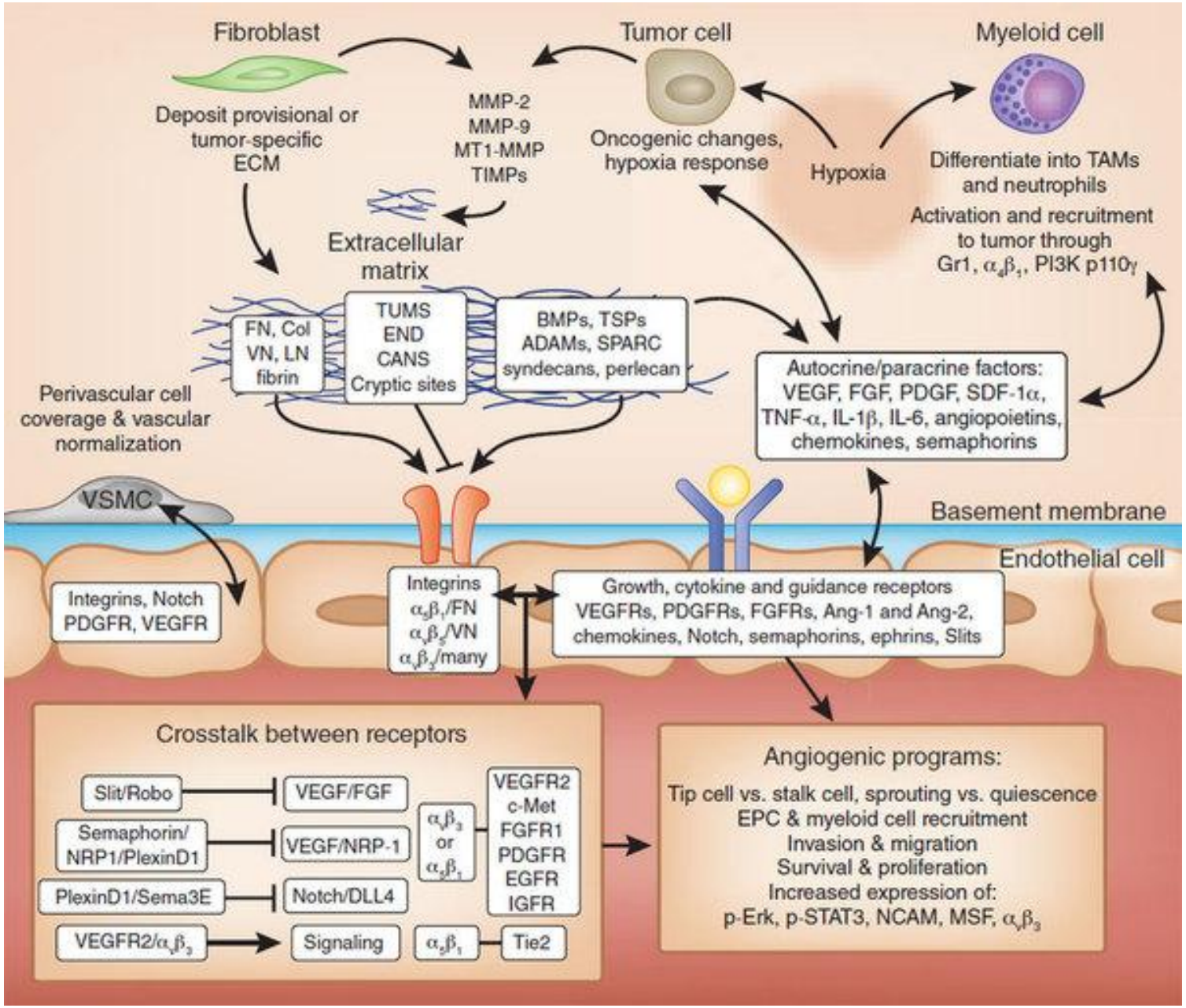

Cell
Differentiation
Cell
Migration
Angiogenic
Stimulus
Cell
Division





Environmental or genetic events transform normal epithelial cells into tumor cells, which grow and divide with little effect on their surroundings until their size exceeds 1–2 mm. At that point, hypoxia and nutrient deprivation trigger the requirement for angiogenesis. Tumor cells release soluble growth factors, chemokines and cytokines, which create a concentration gradient that initiates the sprouting and proliferation of formerly quiescent endothelial cells on nearby blood vessels and lymphatics. These signals also recruit fibroblasts that deposit a repertoire of ECM proteins and enzymes in an attempt to remodel and repair the site. Most tumors elicit an inflammatory response that attracts myeloid cells into the tumor microenvironment, and these cell types release their stores of soluble factors to escalate the angiogenic response. This microenvironment continually changes and evolves as the tumor grows, creating localized pockets of hypoxia, inflammation and ECM turnover that affect blood vessel growth, remodeling and maturation (Weis & Cheresh, 2011).





Weis & Cheresh, 2011

Rip-Tag transgenic mouse: pancreatic islet tumor

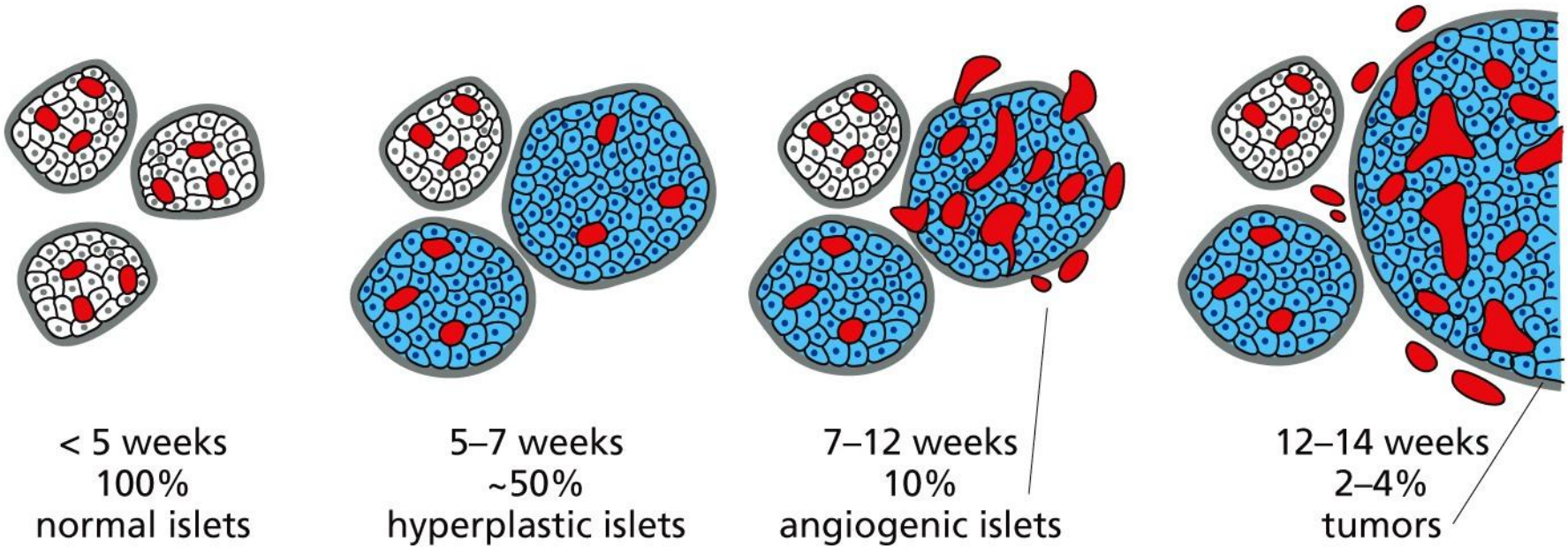


Figure 13.36 The Biology of Cancer (© Garland Science 2014)

Rip-Tag transgenic mouse: SV40 large and small T antigens under insulin promoter control

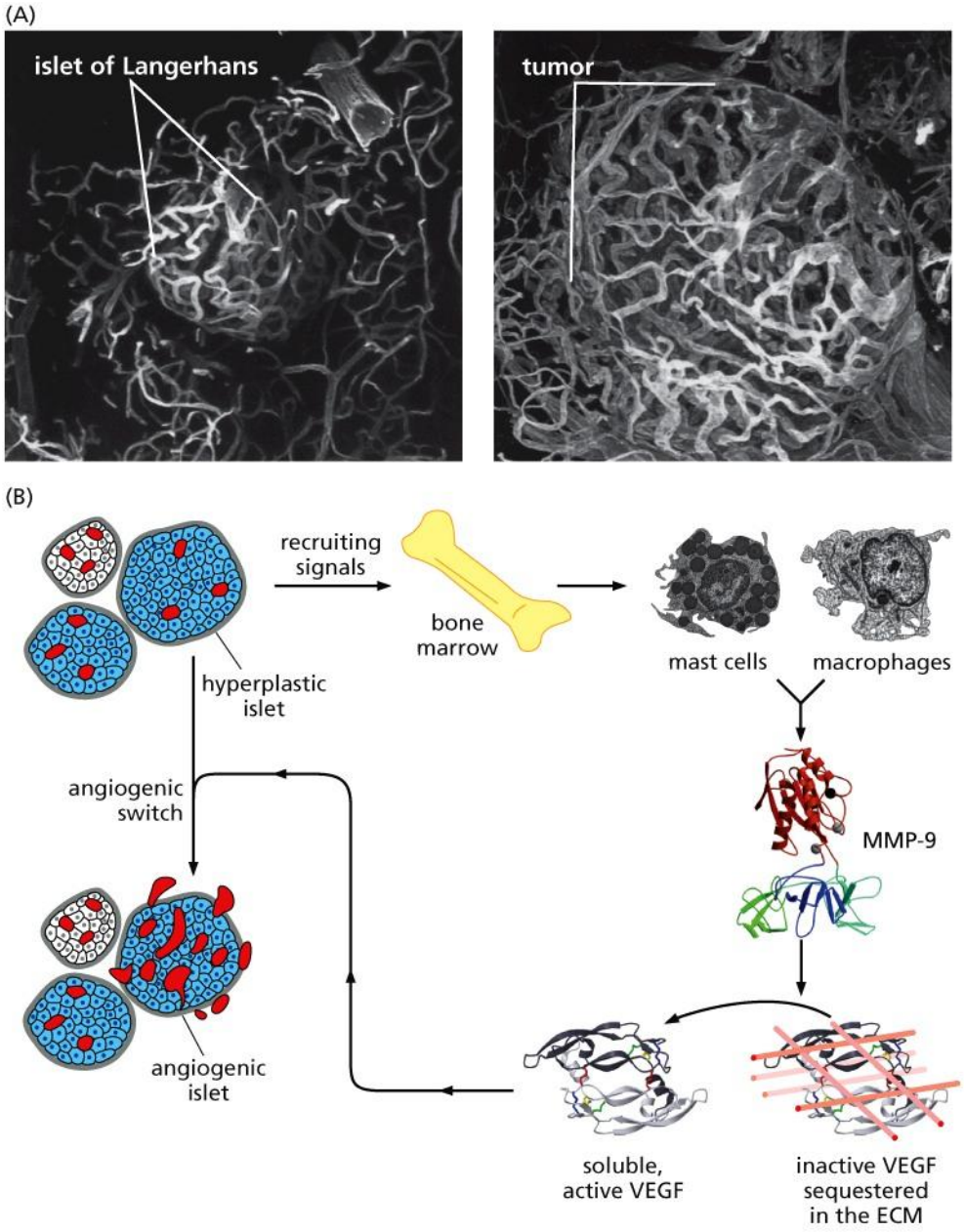
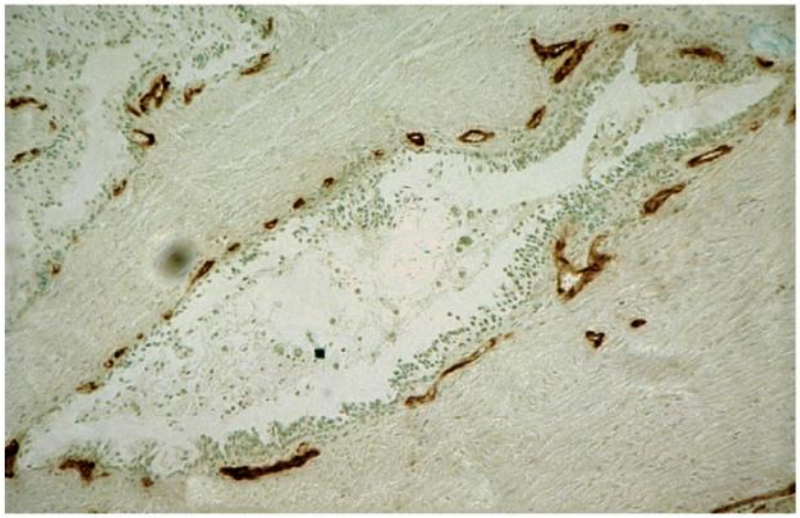


Figure 13.37 The Biology of Cancer (© Garland Science 2014)

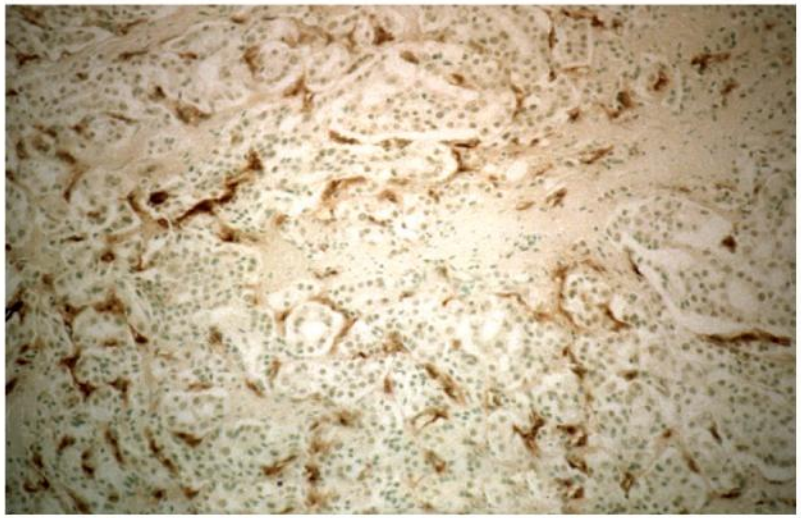
Table 13.3 Important angiogenic factors

Name	Mol. wt. (kD)
Vascular endothelial GFs (VEGFs)	40–45
Basic fibroblast growth factor (bFGF)	18
Acidic fibroblast growth factor (aFGF)	16.4
Angiogenin	14.1
Transforming growth factor-α (TGF-α)	5.5
Transforming growth factor-β1 (TGF-β1)	25
Tumor necrosis factor-α (TNF-α)	17
Platelet-derived growth factor-B (PDGF-B)	45
Granulocyte colony-stimulating factor (G-CSF)	17
Placental growth factor	25
Interleukin-8 (IL-8)	40
Hepatocyte growth factor (HGF)	92
Proliferin	35
Angiopoietin	70
Leptin	16

(A)

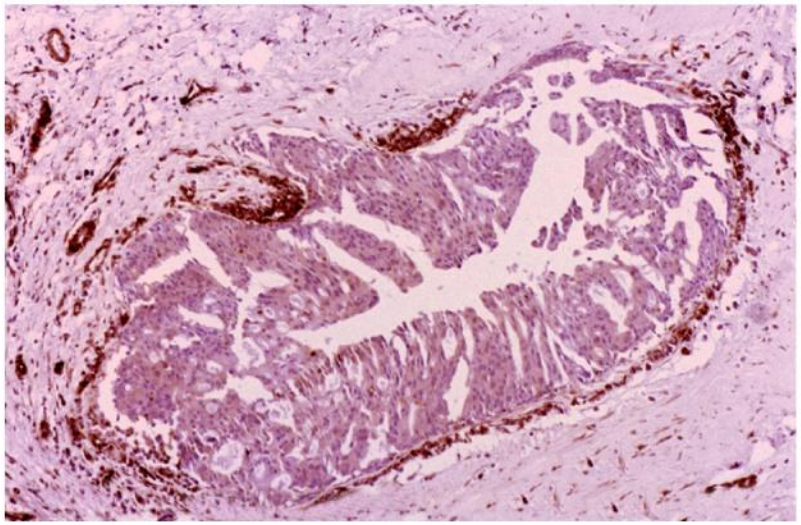


prostate cancer (PIN; *in situ*)

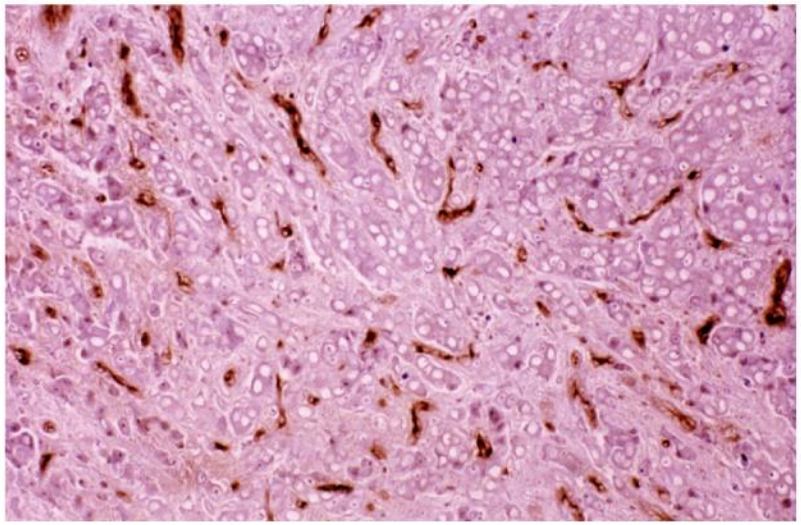


invasive prostate cancer

(B)



human breast cancer (*in situ*)



invasive human breast cancer

Figure 13.40 The Biology of Cancer (© Garland Science 2014)

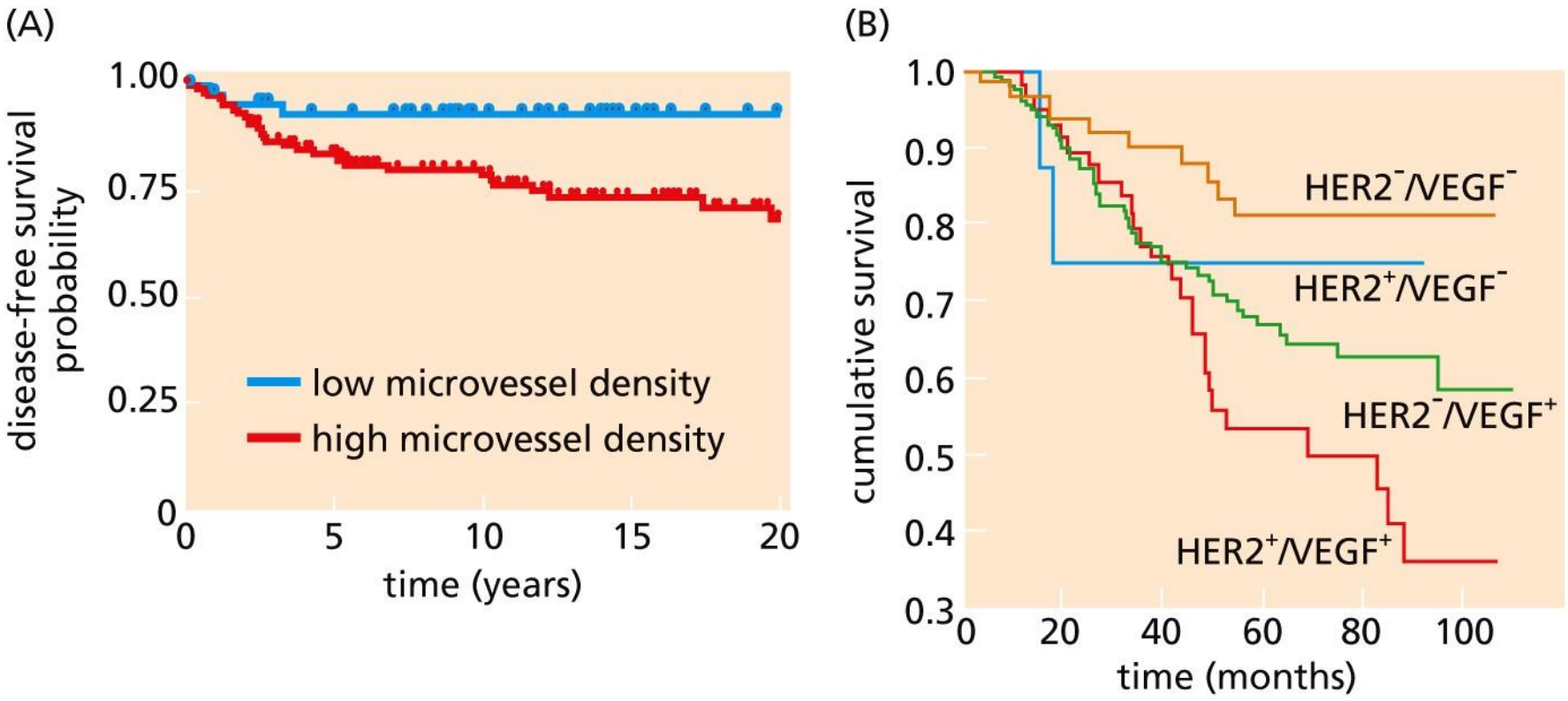


Figure 13.41 The Biology of Cancer (© Garland Science 2014)

Heterogeneous vascularization within a tumor cell population

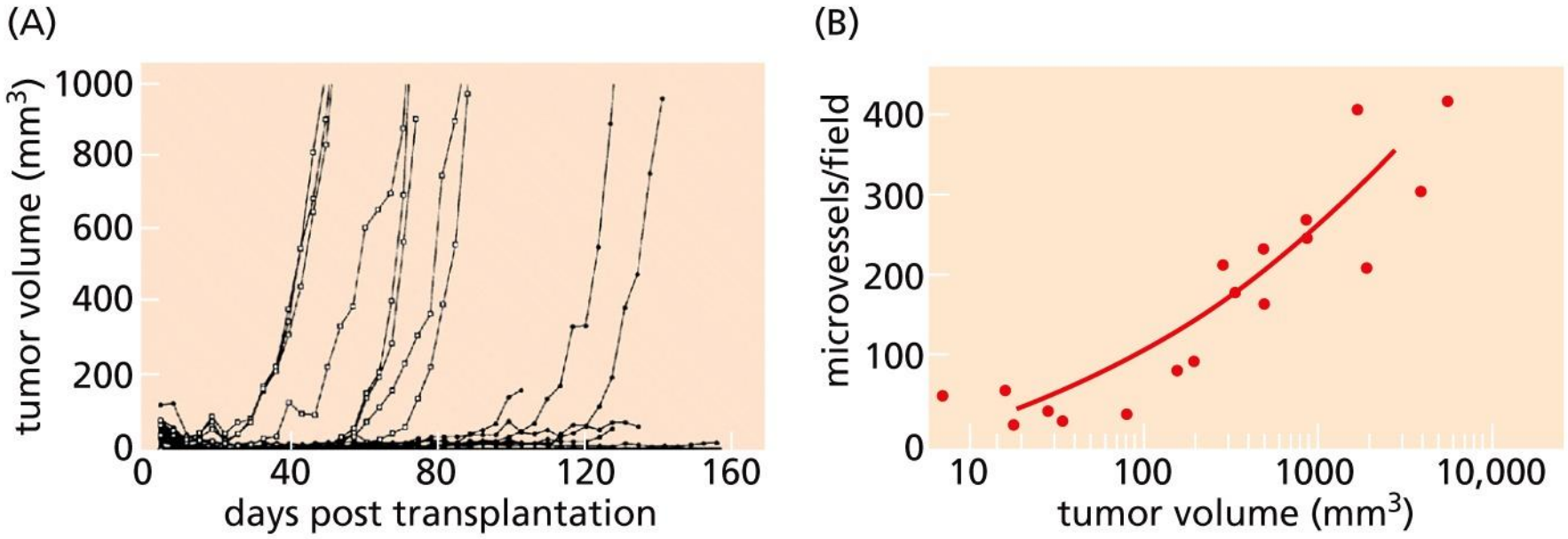


Figure 13.42 The Biology of Cancer (© Garland Science 2014)

Table 13.4 Endogenous inhibitors of angiogenesis

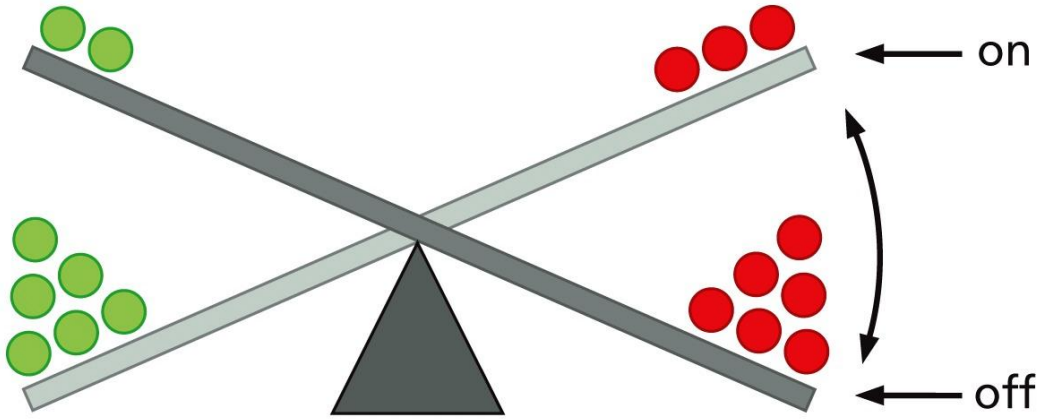
Inhibitor	Description
A. Derived from extracellular matrix	
Anastellin	fragment of fibronectin
Arresten	fragment of type IV collagen α_1 chain of vascular basement membrane
Canstatin	fragment of type IV collagen α_2 chain of vascular basement membrane
Chondromodulin-I	component of cartilage ECM
EFC-XV	fragment of type XV collagen
Endorepellin	fragment of perlecan
Endostatin	fragment of collagen type XVIII
Fibulin	fragment of basement membrane protein
Thrombospondin-1 and -2	ECM glycoproteins
Troponin I	component of cartilage ECM
Tumstatin	fragment of type IV collagen α_3 chain

Adapted from P. Nyberg, L. Xie and R. Kalluri, *Cancer Res.* 65:3967–3979, 2005.

Table 13.4 Endogenous inhibitors of angiogenesis

Inhibitor	Description
B. Non-matrix–derived	
Growth factors and cytokines	
Interferon-α (IFN-α)	cytokine
Interleukins (IL-1β, -12, -18)	cytokines
Pigment epithelium-derived factor (PEDF)	growth factor
Platelet factor-4	released by platelets during degranulation
Other types	
Angiostatin	fragment of plasminogen
Antithrombin III	fragment of antithrombin III
2-Methoxyestradiol	endogenous metabolite of estrogen
PEX	fragment of MMP-2
Plasminogen kringle 5	fragment of angiostatin
Prolactin fragments	specific cleavage fragment
Prothrombin kringle 2	fragment of prothrombin
sFlt-1	soluble form of VEGF-R1 (= Flt-1)
TIMP-2	inhibitor of metalloproteinase-2
TrpRS	fragment of tryptophanyl-tRNA synthetase
Vasostatin	fragment of calreticulin

Adapted from P. Nyberg, L. Xie and R. Kalluri, *Cancer Res.* 65:3967–3979, 2005.



activators
VEGF-A
VEGF-B, -C
FGF1 (aFGF)
FGF2 (bFGF)
other FGFs
etc.

inhibitors
thrombospondin-1, -2
interferon α/β
angiostatin
endostatin
collagen IV fragments
etc.

Figure 13.45 The Biology of Cancer (© Garland Science 2014)

Table 13.6 Summary of clinically approved anti-angiogenic drugs[a]

Agent	Nature of agent	Approved indication	% of patients responding[b]	Improvement[b] in PFS (months)	Improvement[b] in OS (months)
Bevacizumab (Avastin)[c]	anti-VEGF-A MoAb	metastatic CRC[d,e]	10	4.4	4.7
			0	1.4	1.4
			7.8	2.8	2.5
			14.1	2.6	2.1
		metastatic non-squamous NSCLC[d] (with chemotherapy)	20	1.7	2.0
			10.3–14.0	0.4–0.6	NR
		metastatic breast cancer (with chemotherapy)	15.7	5.9	NS
			9–18	0.8–1.9	NS
			11.8–13.4	1.2–2.9	NS[d]
			9.9	2.1	NS
		recurrent GBM[f]	28		2–3
		metastatic RCC[d] (with IFN-α)	18	4.8	NS
			12.4	3.3	NS
Sunitinib (Sutent)[c]	inhibitor of RTKs[g]	metastatic RCC[c]	35	6.0	4.6
		GIST[e]		4.5	
		pancreatic neuroendocrine tumors[c]		4.8	

Table 13.6 (part 1 of 2) The Biology of Cancer (© Garland Science 2014)

Table 13.6 Summary of clinically approved anti-angiogenic drugs[a]

Agent	Nature of agent	Approved indication	% of patients responding[b]	Improvement[b] in PFS (months)	Improvement[b] in OS (months)
Sorafenib (Nexavar)	inhibitor of VEGF-R, cRaf, PDGF-R, and Kit TKs[h]	metastatic RCC[d]	8	2.7	NS
		unresectable HCC[d]	1	NS	2.8
			2	1.4	2.3
Pazopanib (Votrient)	inhibitor of RTKs[i]	metastatic RCC[d]	27	5.0	NR
		soft tissue sarcoma[e]		3.0	
Vandetanib (Caprelsa)	inhibitor of VEGF-R, EGF-R, and Ret TKs	metastatic medullary thyroid carcinoma[d]		6.2	
Axitinib[e] (Inlyta)	inhibitor of VEGF-Rs, PDGF-R and Kit TKs	advanced RCC[e]		2.0	

[a]"Clinically approved" indicates approval for use by the U.S. Food and Drug Administration (FDA). "Inhibitor" indicates in all cases a low molecular weight pharmacologic agent. In addition, as of March 2011, derivatives of thalidomide have been found to have substantial therapeutic utility in treating multiple myeloma; they are not included here, however, because the drugs have adverse physiologic effects, notably neurotoxicity. The mTOR inhibitor Everolimus has been approved for treatment of a series of different tumor types and has anti-angiogenic effects; it has not been listed here because it also has effects on apoptosis, nutrient uptake, and proliferation that may explain part or most of its effects.
[b]Improvement relative to standard treatment.
[c]FDA approval for use against breast cancer was revoked in 2011.
[d]First-line therapy.
[e]Second-line therapy. Axitinib was approved because PFS was 2.0 months longer than existing Sorafenib treatment.
[f]Monotherapy.
[g]Inhibitor of VEGF-R, PDGF-R, FLT-3, Ret, and Kit TKs; Raf/B-Raf.
[h]Low–molecular-weight inhibitor of VEGF-Rs and PDGF-Rs.
[i]Inhibitor of VEGF-Rs, PDGF-Rs, and c-Kit TKs.
Abbreviations: CRC, colorectal cancer; GBM, glioblastoma multiforme; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; IFN, interferon; MoAb, monoclonal antibody; NR, not reported; NS, not significant; NSCLC, non-small-cell lung carcinoma; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RTK, receptor tyrosine kinase.
Table adapted from P. Carmeliet and R. Jain, *Nature* 473:298–307, 2011.

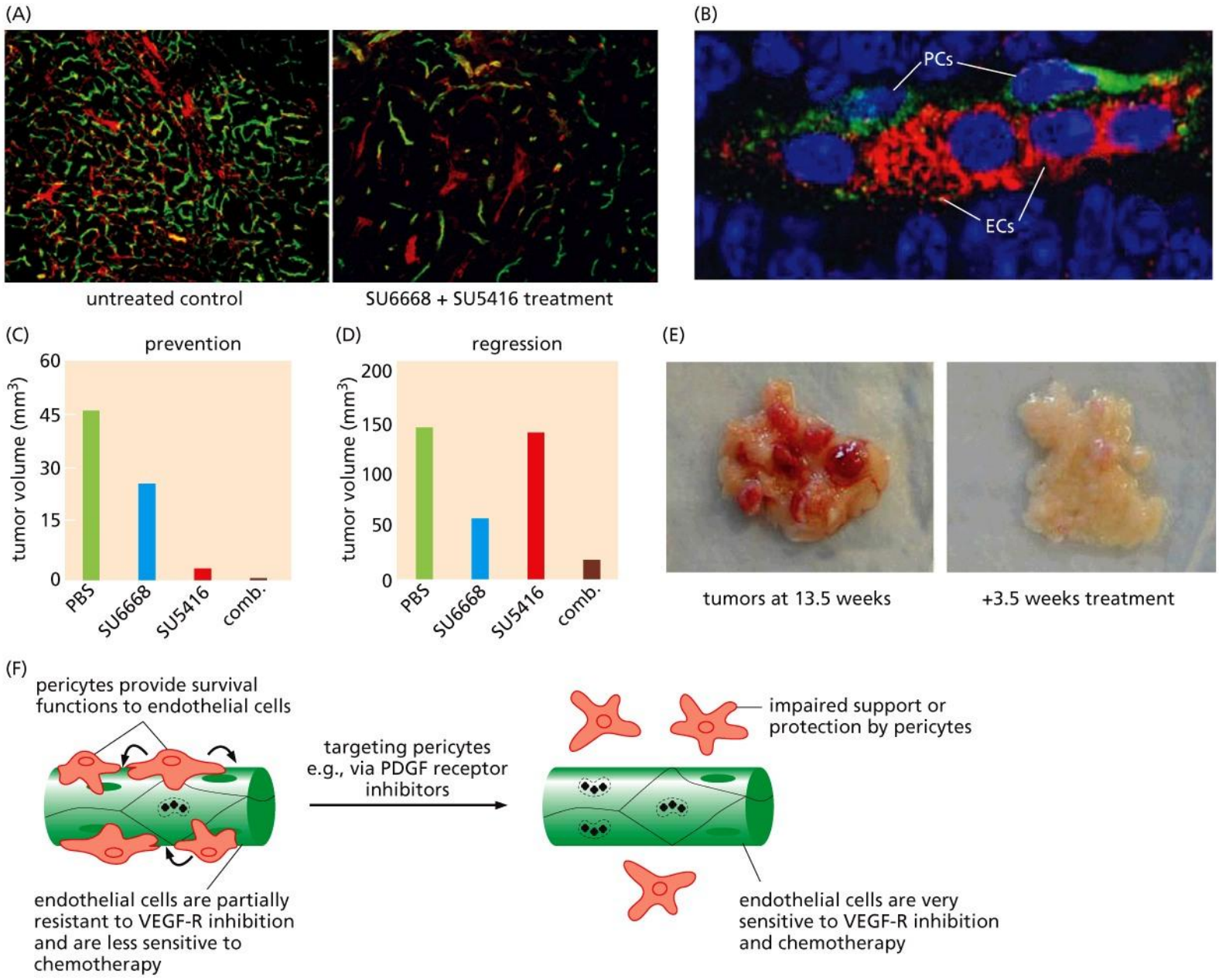


Figure 13.46 The Biology of Cancer (© Garland Science 2014)

Heterotypic interactions as targets for therapy

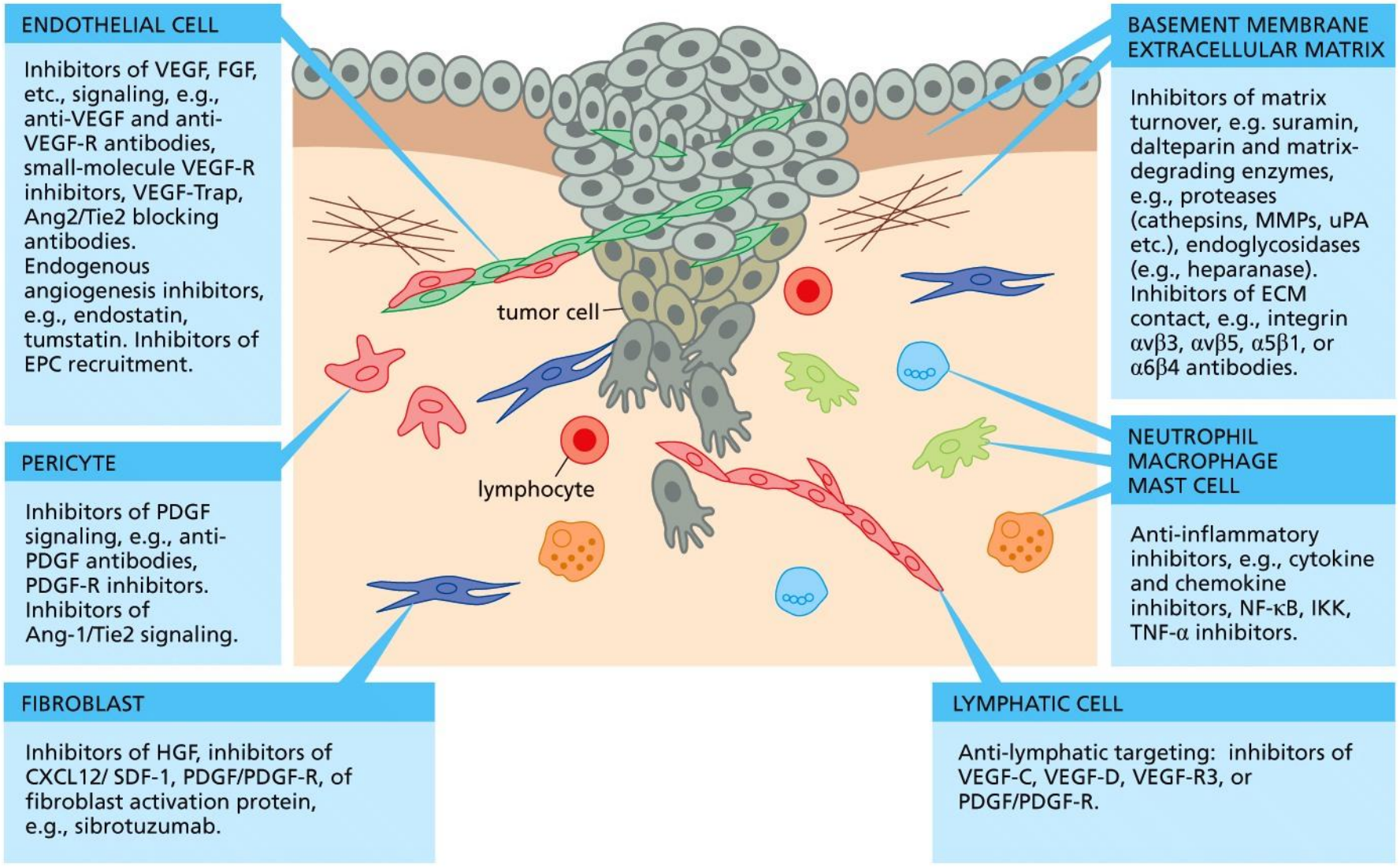
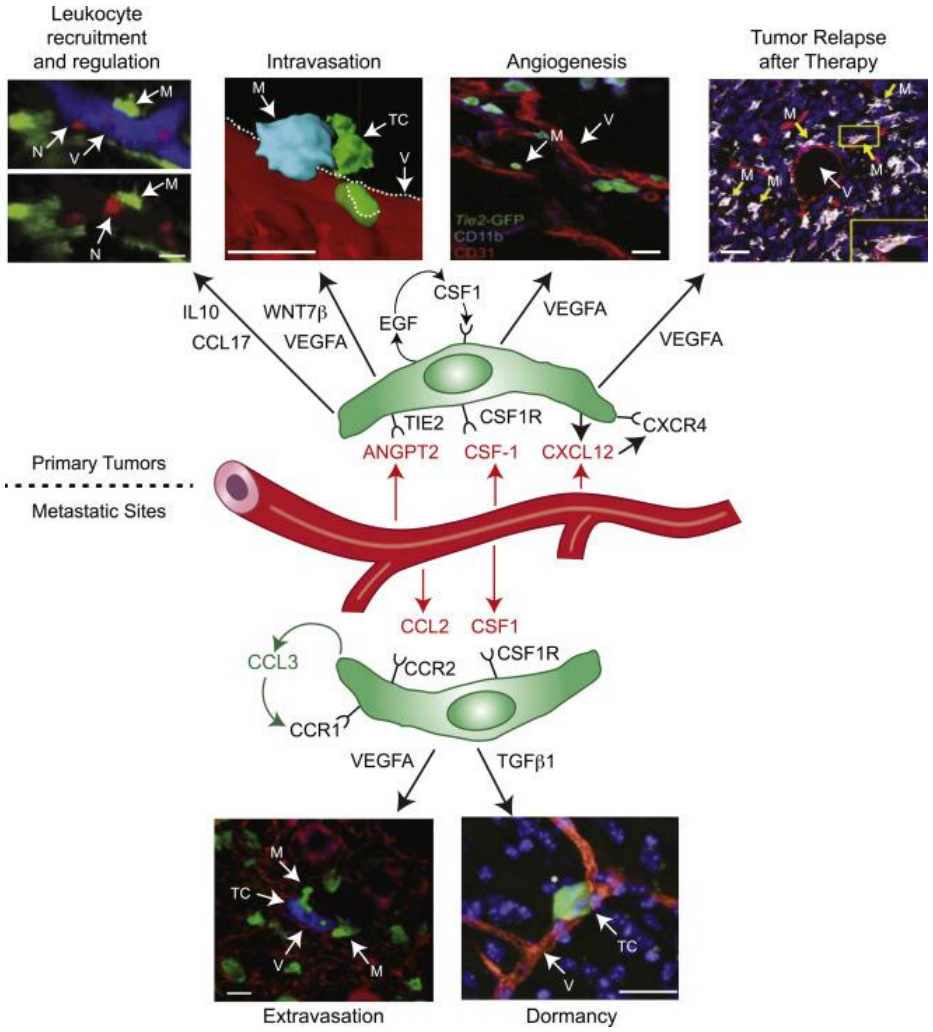


Figure 13.49 The Biology of Cancer (© Garland Science 2014)



The Roles of Perivascular Macrophages in Tumor Progression

In primary tumors. Recruitment and regulation of other tumor-promoting leukocytes – the two images, with and without vessels (blue) included, show that neutrophils (red, N) extravasate in inflamed tissues in close proximity to perivascular (PV) macrophages (green, M). [Reprinted with permission: Abtin et al., 2014.] Intravasation of tumor cells: the images show a triad of a PV TIE2^{+}VEGFA^{+} TAM (blue, M), cancer cells (green, TC), and endothelial cells (red). [Reprinted with permission: Harney et al., 2015.] Angiogenesis stimulation: the image shows TIE2^{+} TAMs (green, M) located near blood vessels (red, V) in tumors. [Reprinted with permission: De Palma et al., 2003.] Relapse of tumors after therapy: the images show a subcutaneous Lewis lung carcinoma after treatment with cyclophosphamide (TIE2^{+} blood vessels [red, V]; TIE2^{+}MRC1^{+} TAMs [white/pink, M]; and cell nuclei [blue]). Inset: a single, TIE2^{+}MRC1^{+} TAM (white/red). [Reprinted with permission: Hughes et al., 2015.] *In metastatic sites*. Extravasation of cancer cells: the image shows a cancer cell (blue, TC), PV macrophages (green, M), and blood vessels (red, V) in the lungs of mice. [Reprinted with permission: Qian et al., 2009.] Dormancy: the image shows a dormant cancer cell (green, TC; white asterisk) located close to a blood vessel (red, V) in the brain. Cell nuclei are shown in blue. [Reprinted with permission: Ghajar et al., 2013.] Many of the above functions involve the release of soluble factors by PV macrophages (green), and often activated by factors expressed by neighboring endothelial cells (red). Scale bars, 20 μm (**Lewis et al., 2016**).